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EDITORIAL COMMENT

Separating the VAT From the FAT

New Insights Into the Cardiometabolic Risks of Obesity*

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Obesity has long been recognized as a risk factor for the development of cardiovascular and metabolic disease including hypertension, insulin resistance and diabetes, and atherogenic dyslipidemia. In 1988, Reaven (1) noted that these risk factors tend to cluster to form a syndrome defined by a unifying pathophysiology leading to multiplicative risk for atherosclerotic cardiovascular disease, which he called *Syndrome X*. Over a decade later, the National Cholesterol Education Program's Adult Treatment Panel III report codified this observation as the metabolic syndrome (MetS) and highlighted abdominal obesity, specifically increased waist circumference (WC), as a major component of the syndrome (2). Although the health risks associated with obesity are clear, there is an emerging appreciation that obesity per se, as defined by simple anthropometric measures such as WC or body mass index (BMI), is neither necessary nor sufficient to promote MetS and its consequences. Rather, it appears that risk for cardiometabolic disease varies substantially across different fat depots, and that an excess of visceral adipose tissue (VAT) may be a primary driver of the metabolic and cardiovascular complications of obesity. An increase in VAT is thought to reflect the inability of the subcutaneous adipose tissue (SAT) depot to sufficiently expand its clearance and storage capacity in response to caloric excess, leading to ectopic fat deposition in the viscera, liver, heart, and skeletal muscle, with pro-inflammatory effects leading to the pathophysiological alterations observed in MetS.

Although an increased WC identifies individuals at increased risk for atherosclerosis (3) and mortality across different levels of BMI (4), WC is an imprecise surrogate for the VAT phenotype. First, the correlation between WC and VAT is highly variable among different racial/ethnic groups, prompting the International Diabetes Federation to define lower cutoffs for abnormal WC in Asian populations (5). Second, measurement of WC includes both VAT and SAT compartments. These 2 depots are anatomically and physiologically distinct, especially within the obese population, and are differentially associated with markers of cardiometabolic risk (6). VAT, but not SAT or WC, has been shown to associate with incident diabetes in obese adults (7) and has been linked to increased risk for the development of cardiovascular disease and cancer (8). Emerging from these data is the concept that the burden of VAT, rather than increased abdominal girth, is central to the pathogenesis of cardiometabolic disease.

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Despite progress in characterizing obesity subphenotypes based on visceral versus subcutaneous adiposity, several key knowledge gaps remain. Because few serial data are available evaluating *changes* in VAT and SAT over time, it is unknown whether the VAT depot is plastic and modifiable independently of more general alterations in body mass. Moreover, data are lacking on how longitudinal changes in VAT and SAT relate to cardiometabolic risk. In this issue of *iJACC*, Shah et al. (9) address these critical knowledge gaps using data from the Multi-Ethnic Study of Atherosclerosis. They measured VAT and SAT area by computed tomography (CT) in 1,511 participants and evaluated cross-sectional associations between abdominal fat depots and cardiometabolic risk markers across BMI categories. In these analyses, the authors confirmed

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previous observations that VAT and SAT are only weakly correlated and reflect divergent risk profiles. Although VAT was associated with an adverse metabolic phenotype characterized by atherogenic dyslipidemia, hyperglycemia, an altered adipocytokine profile, and increased coronary artery calcification, SAT was associated with markers of general adiposity and a lower coronary calcium score, consistent with prior findings (6).

In the most novel component of their study, the authors performed repeat CT assessment of VAT and SAT on 253 participants without MetS at baseline approximately 3 years after the initial examination. They observed that changes in weight were generally minor (median 0.3% [interquartile range (IQR): −3% to 3%]) compared with considerably larger changes in visceral (7% [IQR: −8% to 23%]) and subcutaneous fat (6% [IQR: −6% to 19%]). Furthermore, the correlation between changes in VAT and SAT was modest, suggesting that changes in one fat depot may not parallel changes in the other. Both baseline VAT and changes in VAT associated with incident MetS in fully-adjusted models. In contrast, changes in SAT did not independently associate with MetS. Notably, neither waist circumference nor triglyceride level associated with MetS in the fully-adjusted model, suggesting that their role in the MetS definition may be only as a crude reflection of VAT burden. Overall, these findings suggest that an increase in visceral adiposity impacts cardiometabolic risk rather than weight gain in general and that, as the authors succinctly state, "visceral adiposity is a BMI-independent, dynamic, mechanistic hallmark of cardiometabolic disease."

The study by Shah et al. (9) does have important limitations. The abdominal fat depot assessments were performed post-hoc using CT images that were not prospectively designed for fat quantification. This resulted in substantial missing imaging data requiring imputation. Also, only 17% of participants were included in the serial CT substudy, introducing issues of generalizability and selection bias for the most novel findings of the study. Most importantly, the selection of MetS as the study endpoint limits the clinical implications of the findings. The value of predicting or reclassifying the hazard for this cluster of risk factors is not as evident as for incident disease outcomes such as diabetes or atherosclerotic cardiovascular disease. Despite these limitations, this study provides important new insights into the understanding of the cardiometabolic risks of obesity.

The finding that relatively larger changes in abdominal fat may occur with smaller changes in weight are provocative and demonstrate the substantial "plasticity" of abdominal fat depots, especially VAT. This also highlights the importance of assessing changes in VAT in addition to weight, as accounting for only the latter may overlook biologically-relevant changes in adiposity. These findings also prompt other questions about the biology of abdominal fat. For example, what drives this plasticity? Why do some individuals deposit large amounts of ectopic fat at relatively low BMI, whereas in others, the subcutaneous depot is able to expand adequately and protect against ectopic fat deposition? Are these determinants solely genetic or can alterations in dietary and physical activity behaviors impact fat distribution? Would targeted reduction of VAT without affecting SAT or muscle mass have a salutary effect on cardiometabolic risk?

Although much remains to be learned, the findings from Shah et al. (9) and other recent studies suggest a path forward. First, the scientific community should recognize that BMI and WC in isolation are not sufficiently comprehensive measures of adiposity-related risk in the individual patient. Abnormal fat distribution reflective of more pervasive adipose tissue dysfunction should emerge as a complementary prevention and treatment target. Second, simpler and less expensive ways to accurately assess ectopic/visceral adiposity are sorely needed to better characterize cardiometabolic risk, as CT and magnetic resonance imaging measures may not be practical for widespread use. Until simpler measures are available, other mitigating factors should be taken into account when assessing adiposity-related cardiometabolic risk, including race/ethnicity, behavioral barriers such as poor physical activity and nutritional choices, and evidence for metabolic dysfunction beyond the specific MetS criteria such as the presence of fatty liver disease or sleep-disordered breathing. Third, the focus on patient care should shift from the ambiguous, failure-prone, and potentially stigmatizing recommendation of generalized weight loss to more targeted interventions to prevent VAT gain or support VAT loss. Clinical trials of lifestyle interventions, pharmacologic agents, and bariatric surgery should transition from an overly simplistic focus on changes in body mass to also consider approaches to reduce ectopic and dysfunctional adiposity. These studies should embed serial abdominal imaging in their protocols to delineate which therapies are most effective in reducing the burden of VAT and other ectopic depots. It may finally be time to "separate the VAT from the fat," recognizing abnormal fat distribution as a key

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pathophysiologic driver of MetS. Clinical and investigative efforts should increasingly address the epidemics of obesity, sedentary lifestyle, and nutritional excess within a framework of ectopic/visceral adiposity to reduce the burden of metabolic and cardiovascular disease.

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